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Assistant Commissioner for Patents
Washington, D.C. 20231

On Nov. 28, 2001

TOWNSEND and TOWNSEND and CREW LLP

By: *Stephen J. Karlik*

PATENT
Attorney Docket No.: 15270-004300US
Client Reference No.: 00188-US-NEW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

S. A. Rubin et al.

Application No.: 09/010,377

Filed: January 21, 1998

For: TREATMENT OF VIRAL
ENCEPHALITIS BY AGENTS
BLOCKING ALPHA-VLA-4
INTEGRIN FUNCTION

Examiner: Philip Gambel

Art Unit: 1644

DECLARATION OF STEPHEN J.
KARLIK

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Stephen J. Karlik, state as follows:

1. I, Stephen J. Karlik, am a Professor, University of Western Ontario, London, Ontario, Canada, and am an expert in the field of animal models for multiple sclerosis and other inflammatory disorders.

2. I have reviewed the relevant portion of the subject patent application and the Office Action dated July 31, 2000. The application has claims directed to methods of treating viral encephalitis in a patient free of multiple sclerosis using an agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. I

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understand that the Examiner has cited the following references in rejecting the claimed invention as allegedly being obvious: Bendig et al. (U.S. Patent No. 5,840,299), Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996), and Soilu-Hanninen 1997 (J. Neuroimmunol. 72:95-105, 1997). I understand the Examiner has asserted that the models described in the cited references would have been predictive of the success of the presently claimed methods, and that the present claims are thus obvious in view of the cited references. Applicants have argued that these models would not have been predictive of the success of anti-VLA4 agents in treating viral encephalitis, as the animal models described in the cited references would not have been sufficiently predictive for the treatment of viral encephalitis in the absence of multiple sclerosis. My opinion is that the animal models discussed in the cited references are not predictive of the efficacy of anti-VLA4 agents in viral encephalitis in the absence of multiple sclerosis, that the animal model described in the present application specification is different from the models described in the cited references, and that the animal model of the application is predictive that agents to VLA-4 are useful in treating simple viral encephalitis. My opinion is based on the following facts.

3. The animal models discussed in the cited references show that antibodies to alpha-4 integrin are effective in inhibiting inflammation due to EAE, which is a syndrome simulating multiple sclerosis. However, multiple sclerosis is an autoimmune disease, and the inflammation present in EAE models results primarily, if not exclusively, from nonviral sources. For example, in Soilu-Hanninen's mice, EAE is induced by body irradiation and subsequent immunization with spinal cord homogenate; viral infection serves merely to augment the inflammatory response due to other factors. The avirulent Semliki virus alone does not induce encephalitis. The beneficial results from treatment with antibodies to alpha-4 integrin in Soilu-Hanninen's model may have been entirely or principally due to inhibition of inflammation resulting from the radiation and injection of brain homogenate rather than inhibition of inflammation resulting from viral infection. In the EAE model of Bendig et al., inflammation was due solely to irradiation and subsequent immunization, and thus the viral inflammation could not have been addressed in this model. Therefore, results from EAE models do not directly address the

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ability of antibodies to alpha-4 integrin to treat inflammation that is due exclusively to viral infection.

4. Inflammation that is solely due to viral infection presents great uncertainties for immunosuppressive treatment because of the complex role of inflammation clearing the virus and the resulting damage to surrounding tissues caused by such clearance. The combination of the beneficial and harmful consequences of viral infection-induced inflammation create uncertainty in the predictability of the immunosuppressive agents that would be useful in inhibiting such inflammation. For example, if treatment with an immunosuppressive agent increased the extent of viral infection as a result of decreased immune surveillance, the agent could effectively cause an increase in the damage to the subject. In fact, many immunosuppressive drugs currently prescribed by physicians have a warning label stating that immune suppression could increase susceptibility to infection.
5. The present application differs from the cited references in describing results from a model in which inflammation is solely the result of viral infection. Treatment with $\alpha 4$ integrin antibody was effective in preventing or ameliorating immune-mediated CNS damage following viral encephalitis in rats (see, e.g., pages 23-27). The effects included a reduction in prevalence and severity of clinical Borna disease, a reduction in body weight loss, and a reduction in the severity of encephalitis. Despite blocking the immunopathological immune response to viral encephalitis, the treatment did not cause enhanced viral replication (see, e.g., pages 27-28). These results indicate that treatment with antibodies to alpha-4 integrin is effective in suppressing the harmful effects of virally-induced inflammation without significantly suppressing the beneficial effects that keep viral replication in check.
6. In my opinion, this differential effect in suppressing harmful effects of inflammation without impairing beneficial effects resulting from treatment of simple viral infection with agents to alpha-4 integrin was not reasonably predictable from the animal models discussed in the references cited by the Examiner.

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7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date Nov 19, 2001

By 

Stephen J. Karlik, Ph.D.

Attachments: curriculum vitae
PA 3162994 v2

Stephen James Karlik
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London Health Sciences Centre
University Campus
339 Windermere Road
London, Ontario, N6A 5A5
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EDUCATION:

- 1969 Senior Matriculation, Assumption College School, Windsor
- 1972 BSc (Chemistry) McGill University, Montreal
- 1979 PhD (Physiology) University of Toronto, Toronto
 Thesis Title: Aluminum Interactions with DNA and other Polynucleotides
 Supervisor: Dr. Donald R. Crapper-McLachlan

POST DOCTORAL:

- 1979-1983 Visiting Associate, Laboratory of Cellular and Molecular Biology, National Institutes of Health,
 National Institute on Aging - Director: Dr. G.L. Eichhorn

ACADEMIC / EMPLOYMENT HISTORY:

PRIMARY APPOINTMENTS:

- 1983-1988 Assistant Professor, Department of Diagnostic Radiology and Nuclear Medicine, University of
 Western Ontario, London, Ontario
- 1988-1996 Associate Professor, Department of Diagnostic Radiology and Nuclear Medicine, University of
 Western Ontario, London, Ontario
- 1996-Present Professor, Department of Diagnostic Radiology and Nuclear Medicine, University of Western
 Ontario, London, Ontario

CROSS APPOINTMENTS:

- 1983-1989 Assistant Professor, Department of Clinical Neurological Sciences, University of Western Ontario
 London, Ontario
- 1987-Present Scientist, Imaging Research Laboratory, Robarts Research Institute, London, Ontario
- 1988-1996 Associate Professor, Department of Physiology, University of Western Ontario, London, Ontario
- 1988-Present Honorary Lecturer, Department of Medical Biophysics, University of Western Ontario
- 1989-1996 Associate Professor, Department of Clinical Neurological Sciences, University of Western Ontario,
 London, Ontario
- 1996-Present Professor, Department of Clinical Neurological Sciences, University of Western Ontario,
 London, Ontario
- 1996-Present Professor, Department of Physiology, University of Western Ontario, London, Ontario
- 1996-Present Honorary Lecturer, Department of Pathology, University of Western Ontario, London, Ontario

CONTINUING EDUCATION:**CONFERENCE AND PROFESSIONAL ANNUAL MEETING ATTENDANCE:**

- 1977 Clinical Research Society of Toronto, Toronto
Canadian Congress of Neurological Sciences
- 1979 Canadian Congress of Neurological Sciences
XIth Internal Union of Biochemistry, Toronto
American Chemical Society
Gerontological Society
- 1981 American Society of Biological Chemistry
Federation of American Society of Biological Chemists
- 1982 Canadian Chemical Congress
American Chemical Society
- 1983 International Society of Magnetic Resonance
Aluminum Analysis in Biological Materials
- 1984 Society of Magnetic Resonance in Medicine, New York
American College of Neurology
- 1985 Canadian Association of Radiologists
Radiological Society of North America
Society for Magnetic Resonance Imaging
- 1986 Canadian Congress of Neurological Sciences
XII Symposium Neuroradiologicum
Radiological Society of North America
Metals, Aging and Alzheimer's Disease
- 1987 Canadian Association of Radiologists
American Association of Physicists in Medicine
Society of Magnetic Resonance in Medicine
VI International Congress of Immunology
- 1988 Society of Magnetic Resonance in Medicine
Society of Magnetic Resonance Imaging
- 1989 Society for Magnetic Resonance in Medicine
American Society for Neuroradiology
Society for Magnetic Resonance Imaging
American Academy of Neurology
- 1990 XIV Symposium Neuroradiologicum
76th Radiological Society of North America
Society for Magnetic Resonance in Medicine
- 1991 Society of Magnetic Resonance in Medicine
- 1992 Society of Magnetic Resonance in Medicine
Canadian Association of Radiologists
78th Radiological Society of North America

- 1993 XVII Canadian Congress of Neurological Sciences
Society of Magnetic Resonance in Medicine
79th Radiological Society of North America
Canadian Association of Radiologists
- 1994 IBC Cell Adhesion Meeting
Canadian Association of Radiologists
80th Radiological Society of North America
Society of Magnetic Resonance in Medicine
- 1995 Multiple Sclerosis Load Evaluation Workshop
Society for Neuroscience
Canadian Congress of Neurological Sciences
Canadian Heads of Academic Radiology
- 1996 Asian Pacific Congress on Vascular Disease
IBC Cell Adhesion Molecules and Matrix Proteins
Radiological Society of North America
America's Committee for Treatment and Research in Multiple Sclerosis
Society for Experimental Neuropathology
American Neurological Association
Canadian Heads of Academic Radiology
- 1997 IBC Cell Adhesion Molecules
American Academy of Neurology
- 1998 International Society for Magnetic Resonance in Medicine
American Neurological Association
International Society of Neuroimmunology
Biology of Neurologic Disease Meeting
Society for Health Services Research in Radiology
Canadian Heads of Academic Radiology
Radiological Society of North America
- 1999 Canadian Heads of Academic Radiology
European Society of Neuroradiology
ECTRIMS/ACTRIMS
- 2000 ECTRIMS
RSNA
- 2001 ECTRIMS
ISMRM White Matter Study Group

FACULTY DEVELOPMENT:

- 1995 Conflict Resolution and Confrontation Skills
1996 Organizational Skills Workshop

HONOURS AND OTHER SPECIAL SCIENTIFIC RECOGNITION:

- 1978-1979 Studentship, Ontario Mental Health Foundation
1979-1982 Fogarty Fellowship, National Institutes of Health

1992-1994 Career Scientist, Sterling Winthrop Imaging Research Institute

SCHOLARLY AND PROFESSIONAL ACTIVITIES:

SOCIETY MEMBERSHIPS:

International Society of Magnetic Resonance in Medicine - ISMRM
 American Society of Neuroradiology - ASNR
 Radiological Society of North American - RSNA
 Canadian Association of Radiologists - CAR
 Society for Neuroscience
 Society for Experimental Neuropathology
 Society for Health Services Research in Radiology

NATIONAL SOCIETY EXECUTIVE:

Secretary, 1993 -1998, Radiology Resident's Research Directors, CAR, CHAR
 Chairman, 1998-2000, Radiology Resident's Research Directors, CAR, CHAR

EDITORSHIP:

ACR - CAR Program in Fundamentals of Clinical Research for Radiologists (22 part series and web site)

ROLES ON REVIEW BOARDS OF JOURNALS AND GRANTING AGENCIES:

1. Ad Hoc Reviewer:

<u>Journal</u>	<u>Year(s)</u>
Pharmacology	1985
Inorganic Chimica Acta	1985
Stroke	1985-present
Life Sciences	1987
Medical Physics	1987-present
Magnetic Resonance in Medicine	1989-present
Canadian Journal of Neurological Sciences	1990-present
Annals of Neurology	1990-present
Journal of Magnetic Resonance Imaging	1991-present
Canadian Veterinary Journal	1992-present
Radiology	1997-present

Granting Agency

Medical Research Council of Canada	1985-present
Amiotrophic Lateral Sclerosis Society	1986
Gerontology Research Society of Ontario	1985
Ontario Mental Health Foundation	1987-present
Multiple Sclerosis Society of Canada	1989-present
Ottawa General Hospital Research Fund	1989
Winnipeg Health Sciences Center Research Foundation	1990-present
Sterling-Winthrop Imaging Research Institute	1992-93
Physicians Services Incorporated	1987-present

Fonds de la Recherche du Quebec
Australian Research Council

1993-present
1995-present

2. Member of Study Section

Study Section

Upjohn London Neurosciences Program

Year(s)
1989-91

National Institutes of Health -
National Institutes of Dental Research -
Research Centres in Oral Biology Special Review Committee

1991-1992
1999

Medical Research Council -
Pharmaceutical Manufacturers Association of Canada -
University Industry

1993-present

Ontario Graduate Scholarships

1997-98

Multiple Sclerosis Society of Canada

2000-present

VISITING PROFESSORSHIPS:

- 1) Grantmanship Workshop, McMaster University, 1991.
- 2) Grantmanship Workshop, University of Montreal, 1991.
- 3) Neurology, University of Auckland, New Zealand, 1996.
- 4) Radiology, Queen's University, 2000.

SERVICE TO THE COMMUNITY:

Secretary/Treasurer, St. Mary's Home Support Services 1992 - 1998.

COMMITTEE MEMBERSHIPS:

DEPARTMENT:

- 1) 1993 - Present Resident Research Coordinator, Diagnostic Radiology and Nuclear Medicine, UWO.
- 2) 1993 - Present Residency Training Committee, Diagnostic Radiology and Nuclear Medicine, UWO
- 3) 1988 - Present Radiology Residents Research Director

HOSPITAL:

1. University Hospital: MRI Planning and Building Committee 1985-86.
2. University Hospital: MRI Phase II Planning and Building 1990-91.
3. University Hospital: Chairman, fMRI Planning Committee 1994-95.
4. London Health Sciences, University Campus: Chairman, MRI Upgrade Committee 1997-98.
5. London Health Sciences: Executive, Scholars Forum 1996-1998.

GRADUATE STUDENT AND RESEARCH TRAINEE SUPERVISION:**Student Supervision**

1.	Tom Stavrak	Msc	Physiology	1992	<i>"Permeability Studies on the Blood-Brain Barrier"</i>
2.	Sharon Hyduk	PhD	Physiology	1997	<i>"$\alpha 4$ Integrin in Central Nervous System Inflammation"</i> Recipient of MS Studentship
3.	Judy Karpecki	Msc	Physiology	1999	<i>"Role of Metals in Integrin Adhesion"</i>
4.	Matthew Erskine	Msc	Physiology	1998	<i>"MRI and MRS of MS Patients at 4T"</i>
5.	Paula Piraino	PhD	Physiology	2003	<i>"Prolonged anti $\alpha 4$ treatment in EAE"</i> Recipient of OGSST
6.	Lisa Cook	PhD	Physiology	2003	<i>"Advanced MRI Technologies in MS"</i> Recipient of MS Studentship
7.	Shauna Kirk	MSc	Pathology	2002	<i>"Mechanism of action of beta interferon"</i>

Medical Students 4th Year Elective Research

1.	John O'Brien (Oxford)	1989 - 90	<i>"NMR Changes in EAE Precede Clinical and Pathological Events"</i>
2.	Daniel Struk	1992 - 93	<i>"Stability Studies on Chemoembolization Mixtures"</i>

4th Year Project Students

1.	Charlie Younger	1988 - 89	Chemistry (McMaster)	<i>"Volumetric Determination of MS Plaques in MRI"</i>
2.	Tamara Tram	1989 - 90	Electrical Engineering	<i>"Acquiring EEG in High Field MRI"</i>
3.	John Ieraci	1989 - 90	Electrical Engineering	<i>"Digital Filtering for EEG Measurements in MRI"</i>
4.	Tom Stavrak	1990 - 1	Physiology	<i>"Phosphorus NMR Spectroscopy in Epilepsy"</i>
5.	Jeff Granton	1993 - 4	Physiology	<i>"Role of Superoxide in Brain Inflammation"</i>
6.	Roselyn Jeun	1992 - 3	Physiology	<i>"Prazosin Alters Clinical Progress of EAE"</i>
7.	Eni Kesthelyi	1994 - 5	Physiology	<i>"Anti $\alpha 4$ Treatment of Longstanding EAE"</i>
8.	Jennifer Tomlin	1995 - 6	Physiology	<i>"Extending Anti-$\alpha 4$ Therapy Using Tolerization"</i>
9.	Paula Piraino	1996 - 7	Physiology	<i>"Copaxone Treatment of EAE"</i>
10.	Tomas Jimenez	1997 - 8	Physiology	<i>"Cell Trafficking and BBB Disruption"</i>

Radiology Residents, Research Project

1.	Leslie Vandenburg	1992 - 93	<i>"Chemoembolization mixtures" (Winner CAR Resident's Award)</i>
2.	P.S. Olutola	1985 - 86	<i>"Serum effects of radiographic contrast"</i>

Advisory Committees

1.	Chao Zhong	MSc (Pharmacology)	1989 - 1991
2.	Eugene Florio	PhD (Biochemistry)	1989 - 1992
3.	Ross Mitchell	PhD (Biophysics)	1990 - 1996

4.	Andrew Farrall	MSc (Biophysics)	1992 - 1995
5.	Scott Hamilton	PhD (Physiology)	1992 - 1996
6.	Elizabeth Henderson	MSc (Biophysics)	1993 - 1999
7.	Rob Bartha	MSc (Biophysics)	1994 - 1998
8.	Joseph Gati	MSc (Biophysics)	1995 - 1996
9.	Craig Jones	MSc (Biophysics)	1995 - 1997
10.	Constance Campbell	MSc (Biophysics)	1995 - 1997
11.	Chris Thomas	PhD (Biophysics)	1996 - 2000
12.	Jodi Adams	MSc (Physiology)	1997 - 2000
13.	Cheryl McCreary	PhD (Biophysics)	1998 - present
14.	Neil Duggal	MSc (Pathology)	1998 - 2001
15.	Angela Beye	MSc (Physiology)	1998 - present
16.	Eric Jensen	PhD (Biophysics)	1998 - present
17.	Cameron Lush	PhD (Physiology)	1998 - 2001

Post-doctoral Fellows:

1.	Eric Viiree	1992 - 1994	<u>Current Appointment</u> Dept. Of Otolaryngology and Human Interface Technology Laboratory University of Washington, Seattle
2.	Alan Taylor	1989 - 1990	Department of Chemistry University of Victoria, British Columbia
3.	Paula Gareau	1997 - 2000	Scientist, Imaging Laboratory, Roberts Research Institute Winner: Young Investigator Award ISMRM 2000

Thesis Examiner

1.	Wendy Stewart	PhD	University of British Columbia
2.	Joseph Maglesi	MSc	Biochemistry
3.	Ivan Yeung	PhD	Medical Biophysics
4.	Jeff Stanley	PhD	Medical Biophysics
5.	Cheryl McCreary	MSc	Medical Biophysics
6.	Kathy Hamilton	PhD	Biochemistry
7.	Saryu Singh	PhD	Medical Biophysics
8.	Greet Peersman	PhD	Univ. of Antwerp
9.	Ian Callow	MSc	Pharmacology and Toxicology
10.	Raymond Chung	PhD	Physiology
11.	Susan Hochstenbach	PhD	Physiology
12.	Monica Way	MSc	Neuroscience
13.	Ramin Siushansian	PhD	Physiology
14.	John Potwarka	MSc	Medical Biophysics
15.	Cameron Lush	MSc	Physiology
16.	Jonas Vanderznan	MSc	Physiology
17.	Rob Bartha	PhD	Medical Biophysics
18.	Lin Wang	MSc	McGill University
19.	Xi-Zhen Zhu	PhD	Chemistry
20.	Janine Robichaud	MSc	Microbiology and Immunology
21.	L.Foley	PhD	Biochemistry, James Cook University

CONTRIBUTIONS TO TEACHING AND EDUCATION:**Teaching**

1989 - present	Biology 310 Laboratory	Cardiovascular and Respiratory	15 hrs. Laboratory (groups of 8)
1989 - 1998	Dental Physiology (415)	Respiratory System Seminars	8 hrs. Classroom (n=40)
1993 - present	Critical Inquiry	Radiology Residents	8 hrs. Small Group
			24 hrs. Small Group
1990 - present	Physiology 441y	Seminars	4 hrs. Small Group
1998 - 2000	Oral Physiology (Dentistry 115)	Sensory Physiology Seminars	8 hrs. Classroom n=54
			8 hrs. Small Groups

RESEARCH FOCUS:

I am primarily interested in:

- 1) The generation and evaluation of new therapies for multiple sclerosis.
- 2) The molecular basis of altered MRI/MRS in MS.

RESEARCH FUNDING:

<u>Year</u>	<u>Grantor</u>	<u>Investigators</u>	<u>Purpose</u>	<u>Amount</u>
1983	Academic Development, U.W.O.	Karlik	Start up	65,000
1984-85	Banting Foundation	Karlik	MRI Research	18,700
1984-86	PST	Noseworthy Karlik	EAE-NMR Studies	100,000
1987-92	MS Society	Karlik	EAE-MRI Studies	285,000
1987-89	Lederle Laboratories	Karlik Noseworthy	Quantitation of Mitoxantrone treatment in EAE	30,000
1988-91	Upjohn Co.	Karlik	Lipid peroxidase inhibitors in BBB disease	147,000
1989	Upjohn Co.	Noseworthy Karlik	Quantitative MRI in MS	114,512
1986-90	MRC	Fox, Karlik	MRI of Dementia	117,000
1987-90	MRC	Feasby, Fox, Ebers, Karlik	Optic Neuritis	59,149

1988-89 Heart & Stroke	Gelb, Karlik	Drug Treatment in Stroke	52,079
1984-90 University Hospital Pooled Research Fund, University Hospital Foundation	Karlik	Several small Grants (5) for project initiation	61,250
1989-90 MS Society	Karlik, Noseworthy	Quantitative MRI in MS	110,000
1991-94 Upjohn Co.	Karlik	Lazaroid suppression of EAE	90,965
1992-93 Sterling-Winthrop Imaging Research Institute	Karlik	Cine MRI in oculomotor disease	14,423
1992-94 Sterling-Winthrop Imaging Research Institute	Karlik	Career Scientist	80,509
1992-2002 MS Society	Mitchell, Karlik, Lee, Rutt	Automated Detection and Quantification of MS lesions in MRI Images	420,000
1993-94 Mallinckrodt	Karlik	Quantifying Blood-Brain- Barrier Permeability Using MP1177/10	36,400
1994-95 UH Pooled Research Fund	Downey, Karlik	Intervention Chemical Carcinogens	6,500
1994-96 MS Society	Karlik, Rice	An integrin-based therapy for Multiple Sclerosis	210,000
1994-2004 Athena Neurosciences/Elan	Karlik	Cell Adhesion Studies in EAE	521,000
1995-96 MS Society	Hyduk	Studentship (PhD Student)	15,959
1996-97 Teva Pharmaceuticals	Karlik	Evaluation of Cop-1	25,000
1996-97 Biogen, Inc.	Karlik	Anticytokine therapy in MS	21,000
1997-98 MS Society	Karlik, Rice	MRI and MRS at 4T	33,000
1998-2000 MS Society	Gareau	PDF	50,000
1999-2002 OGSST	Piraino	Studentship	45,000
2000-2003 ACR	Karlik, Reinhold, Beam, Blackmore	Fundamentals of Clinical Research for Radiologists	450,000

2000-2001	CAR Foundation	Karlik, Rankin	Cost of Angiography	20,000
2000-2001	MS Society	Cook	Studentship	16,000
2000-2001	Biogen	Karlik	Immunotherapy in MS	20,200
2001-2004	CIHR	Karlik, Hammond	Remyelination in EAE	110,000

PUBLICATIONS:

CHAPTERS IN BOOKS:

1. Crapper, D.R., Karlik, S.J., and DeBoni, U.: Aluminum and Other Metals in Senile (Alzheimer) Dementia. In Katzman, R., Terry, R.D., and Bick, K.L. (Eds.): Alzheimer's Disease: Senile Dementia and Related Disorders. (Aging, Vol 7). Raven Press, New York, 1978, pp. 471-485.
2. Eichhorn, G.I., Shin, Y.A., Clark, P., Rifkind, J., Pitha, J., Tarien, E., Rao, G., Karlik, S.J., and Crapper, D.R.: Essential and Deleterious Effects in the Interaction of Metal Ions with Nucleic Acids. In Kharasch, N. (Ed.): Trace Metals in Health and Disease. Raven Press, New York, 1979, pp. 123-133.
3. Eichhorn, G.L., Butzow, J., Clark, P., von Hahn, H., Rao, G., Hein, J., Tarien, E., Crapper, D., and Karlik, S.J.: Metal Ion-Nucleic Acid Interactions, Aging and Alzheimer's Disease. In Martell, A. (Ed.): Inorganic Chemistry in Biology and Medicine. American Chemical Society, Washington, D.C., 1980, pp. 75-88.
4. Crapper, D.R., Dalton, A.J., Karlik, S.J., and DeBoni, U.: The Role of Aluminum in Alzheimer's Disease. Chapter 2 in Alexander, P.E. (Ed.): Electrolytes and Neuropsychiatric Disorders. Spectrum Publication, Inc., New York, 1981, p.89.
5. Crapper-McLachlan, D.R., Galen, H., Farnell, B., DeBoni, U., Karlik, S.J., and Eichhorn, G.L.: Aluminum in Human Brain Disease. In Sarkar, B. (Ed.): Metal Ions in Health and Disease. Raven Press, New York, 1983, pp. 209-218.
6. Karlik, S.J. Use of NMR Spectroscopy to Measure Intracellular Ion Concentrations, in Methods in Neurosciences. 27:39-51 (1995).

ARTICLES IN REFEREED JOURNALS:

7. Karlik, S.J. Eichhorn, G.L., and Crapper, D.R.: Molecular Interactions of Aluminum with DNA. Neurotoxicology, 1: 83-88 (1980).
8. Karlik, S.J., Eichhorn, G.L., Lewis, P.N., and Crapper, D.R.: Interactions of Aluminum Species with DNA. Biochemistry, 19: 5991-5998 (1980).
9. Karlik, S.J., Elgavish, G.A., and Eichhorn, G.L.: ²⁷Al-NMR Studies on Phosphorylated Biological Compounds. J. Mag. Res., 49: 164 (1982).
10. Karlik, S.J., Elgavish, G.A., and Eichhorn, G.L.: Multinuclear NMR Studies of Aluminum-ATP Equilibria. Journal of the American Chemical Society, 105: 602-609 (1983).
11. Karlik, S.J., Elgavish, G.A., and Eichhorn, G.L.: ²⁷Al-NMR of Aqueous Aluminum Complexes with Carboxy Ligands. Inorganic Chemistry, 22: 525-529 (1983).
12. Vinitski, S., Pearson, M., Karlik, S., Morgan, W., Carey, L., Perkins, G., and Goto, T.: Differentiation of Parenchymal

Lung Disorders with in vitro proton NMR, *Mag Res Med* 3, 120 (1986).

13. Karlik, S.J.: Common Pharmaceutical Alter Tissue Proton NMR Properties, *Mag Res Med* 3, 366 (1986).
14. Karlik, S.J., Gilbert, J., Strejan, G.G. and Noseworthy, J.H.: NMR studies in Acute Experimental Encephalomyelitis (EAE). Normalization of T1 and T2 with parenchymal cellular infiltration, *Neurology* 36, 1112 (1986).
15. Olutola, P.S., Hutton, L., Karlik, S. and Henderson, A.R.: The Effect of Ionic Radiographic Contrast Medium on Serum Electrolytes and Proteins during Intravenous Urography. *Amer. J. Roent.* 147, 657 (1986).
16. Fox, A.J., Bogousslavsky, J., Carey, L.S., Barnett, H.J.M., Vinitski, S., Karlik, S.J., Vinuela, F., Pelz, D.M., Hachinski, V.: Magnetic Resonance Imaging of Small Medulla Infarctions. *Amer. J. Neuroradiol.* 7, 229 (1986).
17. Chin, J., Stiller C. and Karlik, S.J.: Nuclear Magnetic Resonance Assessment of Renal Perfusion and Preservation for Transplantation. *J. Urol.* 136, 1351 (1986).
18. Pelz, D.M., Karlik, S.J., Fox, A. and Vinuela, F.: Magnetic Resonance Imaging in Down Syndrome. *Can. J. Neurol. Sci* 13:566 (1986).
19. Karlik, S.J., Fuller, J. and Gelb, A.: Anesthetics Alter Tissue Proton Relaxation. *Acta Radiologica* 369:500 (1986).
20. Eichhorn, G.L., Butzow, J.J., Shin, Y.A., Clark, P., Pitha, J., Pillai, R.P. and Karlik, S.J.: Changes of Biological Significance Induced by Metal Ions in the Structure of Nucleic Acids. *Ann. 1st, Super. Sanita*, Vol. 22, N.2 (1986), pp. 663-668.
21. O'Brien, J.T., Noseworthy, J.H., Gilbert, J.J. and Karlik, S.J.: NMR Changes in Experimental Allergic Encephalomyelitis: NMR Changes Precede Clinical and Pathological Events. *Mag. Res. Med.* 5:107 (1987).
22. Karlik, S.J. and Noseworthy, J.H.: Apparatus for Percoll Microgravimetry in Experimental Brain Edema. *Stroke* 18:661 (1987).
23. Grant, C.W.M., Barker, K.R., Florio, E. and Karlik, S.J.: A phospholipid Spin Label used as a Liposome - Associated MRI Contrast Agent. *Mag. Res. Med.* 5, 371 (1987).
24. Noseworthy, J.H., Gilbert, J.J., Vandervoort, M.K. and Karlik, S.J.: Post Natal Changes in Guinea Pig Central Nervous System: Potential Relevance to Experimental Allergic Encephalomyelitis. *Magnetic Resonance in Medicine* 6, 199 (1988).
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3. "NMR Studies in Alzheimer's Disease", McGill University, June 1982.
4. "Multinuclear NMR Studies on Aqueous Aluminum Complexes", Smith Kline French Laboratories, June 1982.
5. "Aluminum, Phosphorus and Proton NMR Spectroscopy on Aqueous Aluminum Complexes", Guelph University, July 1982.
6. "Biological Applications of Multinuclear NMR Spectroscopy", University of Western Ontario, July 1983.
7. "Aluminum in Alzheimer's Disease", Johns Hopkins University, July 1983.
8. "Nuclear Magnetic Resonance Imaging Applications", Symposium, University of Western Ontario, March 1984.
9. "Factors Affecting NMR Imaging", National Institute of Health, June 1984.
10. "Factors Affecting MMR Properties of Tissues", National Institutes of Health, May 1985.
11. "Alterations in Tissue NMR Properties", Symposium, St. Joseph's Hospital Research Institute, London, May 1985.
12. "NMR Studies in Alzheimer's Disease", International Symposium on Organic Dementia, London 1986.
13. "Aluminum and Alzheimer's Disease", National Institutes of Health, Trace Metals, Aging and Alzheimer's Disease, Bethesda 1986.
14. Session Chairman, "Fast Imaging, Clinical". 6th SMRI, Boston, Mass, 1988.
15. "In Vivo Proton T1 and T2 Measurements and Radiological Assessment of MRI Scans in Dementia", Alzheimer's Disease Center of Oregon: New Insights into Aging and Dementia: Imaging Brain Structure and Function, 1989.
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17. Grantmanship Lecture, Canadian Association of Radiologist, Annual Meeting, 1991.
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23. "MRI: Some Practical Considerations", Annual Meeting, Radiology Managers of Ontario, 1995.
24. "Quantitating Lesions in MRI of MS", University of Auckland, New Zealand, 1996.
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27. "Imaging Brain Function and Dysfunction", 2nd Korca - U.S. Joint Workshop on Brain Science, KAIST, Taejon, Korea, January 2000.
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31. "New MRI Findings in Multiple Sclerosis", TEVA Symposium, July 2000
32. "Development of Antegren", Biogen Symposium, August 2001
33. "Evaluation of the Animal Models of MS", Elan Scientific Advisory Board, Sept 2001
34. "Evaluation of the new McDonald Criteria for the Diagnosis of MS" and "Results of Sequential Studies of MRI and MRS in MS", le troisieme preceptorat sur la SEP, 2001

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